11/14/03

REMARKS

An Amendment and Notice of Appeal were filed on April 17, 2003. According to 37 C.F.R. § 1.114 and MPEP § 706.07(h), subsection X, if an applicant files a Request For Continued Examination (RCE) after filing a Notice of Appeal, but prior to a decision on appeal, the RCE will be treated as a request to withdraw the appeal and to reopen prosecution of the application. Thus, Applicants respectfully request that the appeal be withdrawn and that prosecution of the above-identified application be reopen.

1. The Rejection Under 35 U.S.C. §112 First Paragraph, Should Be Withdrawn

Claims 19-21 and 23-24 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. According to the Examiner, the Applicant has not shown that angiostatin could be generated after administering urokinase in a patient having *any* angiogenic disease. As in the final Office Action, dated October 21, 2002, the gravamen of the Examiner's rejection is that it is unpredictable whether the administration of a plasminogen activator alone or in combination with a sulfhydryl donor would generate angiostatin in all angiogenic disease states or be adequate for inhibiting angiogenesis *in vivo* in light of Berman *et al.* 1982, Invest. Opthamal. Vis. Sci. 22:191-199 ("Berman"). According to the Examiner, Berman shows the opposite effect -- *i.e.*, that the administration of urokinase (a plasminogen activator) actually promotes vascularization of the cornea *in vivo* and that it is unpredictable whether the administration of urokinse would not cancel any effect by angiostatin. This rejection is in error and should be withdrawn.

Berman is irrelevant to enablement of the method of the invention because Berman does not use the claimed protocol -- *i.e.*, Berman does not administer a "therapeutically effective amount" of plasminogen activator that increases the amount of angiostatin in the animal. [1] Instead, Berman injects 20µl aliquots of urokinase (3.7 CTA Units) intrastromally into the corneas of 2 to 3.5 kg rabbits (as a bleb about 2 mm on the center from the limbus of contralateral corneas). In contrast, Applicants claim the administration of an amount of plasminogen activator *effective to increase the amount of angiostatin* in the animal to treat the angiogenic disease.

By contrast to the protocol used by Berman, when plasminogen activator is administered in accordance with the claimed methods of the present invention, the amount of angiostatin generated *in vivo* will increase and thereby inhibit angiogenesis. Moreover, Applicants have demonstrated that angiostatin inhibits angiogenesis in corneas. *See,* for example, Reference BS of record, co-authored by the inventor (Gately et al., 1996, Cancer Res. 56: 4887-90, at Fig. 3 and its accompanying discussion at p. 4889, col. 1, last paragraph

[1] In fact Berman does not disclose or suggest the generation of any angiostatin.

bridging over to col. 2)[2], which demonstrates that angiostatin is indeed effective in inhibiting angiogenesis in the cornea. Thus, the Examiner cannot properly rely on Berman to show unpredictability of the claimed method, because Berman's protocol does not use the claimed method.[3]

The present invention is fully enabled because it discloses and claims methods of increasing the amount of angiostatin present in an animal to prevent or inhibit angiogenesis (including angiogenesis of any and all angiogenic diseases) by generating angiostatin via the administration of a therapeutically effective amount of plasminogen activator. The Examiner's contention that Applicants have demonstrated efficacy only for combinations of plasminogen activator with a sulfhydryl donor for the treatment of cancer (Final Office Action, p. 4) is incorrect. In this regard, the Examiner's attention is again invited to the following evidence of record in parent application Serial No. 08/991,761, which the Examiner agreed establishes the following facts: (1) Urokinase alone generates angiostatin in human plasma (Soff Supplemental Declaration dated December 4, 2001, Exhibit 5); (2) Urokinase alone generates angiostatin in human patients (Soff Supplemental Declaration dated February 13, 2001, paragraphs 9, 14, 18 & Exhibit D); (3) the generation of angiostatin has a clinical benefit in human patients with malignant neoplastic disease (Soff Supplemental Declaration dated February 13, 2001, Exhibit B); and (4) when administered without a sulfhydryl donor, the dose and dosage regimen of plasminogen activator can be adjusted to generate levels of angiostatin that have a clinical benefit in patients with malignant neoplastic disease (Second Supplemental Declaration of Gerald A. Soff, M.D., Under 37 C.F.R. § 1.132, dated October 7, 2002). Copies of the Soff Declarations referred to above were enclosed with Applicants previous response filed on April 17, 2003.

In view of the foregoing, the rejection under 35 U.S.C. § 112 should be withdrawn. Thus, Applicants have demonstrated that using the method of the invention, angiostatin is generated in patients, and has a clinical benefit in treating cancer. The Examiner has not supplied any evidence or reason to doubt that such generation of angiostatin in patients would likewise have a clinical benefit in other angiogenic diseases.

As stated in Applicant previous response, in the event that there are any facts relied upon for rejecting any of the pending claims within the personal knowledge of the Examiner or an employee of the United States Patent and Trademark Office, Applicants respectfully request that the Examiner or such employee submit an affidavit attesting to such personal knowledge pursuant to 37 C.F.R. § 1.104(d)(2).

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[2] Reference BS was published subsequent to the September 17, 1996 priority date of the present application.

[3] The Examiner's reliance of Volpert is even less relevant to enablement. Volpert relates to the use of captopril alone. The Applicant has already demonstrated, and the Examiner does not dispute, that combinations of plasminogen activator and captopril inhibit angiogenesis. See ensuing discussion above.

2. **Rejection Under Obviousness-Type Double Patenting**

Applicants note with appreciation the Examiner's indication that the obviousness-type double patenting rejection will be held in abeyance until the claims are otherwise deemed allowable at which time Applicants will file a terminal disclaimer, if appropriate, based on the final version of the claims allowed.

3. **Election Requirement**

The Examiner notes that the application still contains claims drawn to an invention nonelected and that a complete reply to the final rejection must include cancellation of the nonelected subject matter or other appropriate action. In response, the Applicants respectfully note that all of the pending claims fall within previously elected Group V. In the alternative, the Applicants respectfully request that the Examiner specifically point out which claims the Examiner considers to be nonelected.

CONCLUSION

Entry and consideration of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. Applicants believe that the present claims meet all of the requirements for patentability. If any issues remain, the Examiner is requested to telephone the undersigned at (212) 790-6431.

Respectfully submitted,

Laura A. Coruzzi Reg. No.: 30,742

by Brian C. Ramm Reg. No: 48,176

Date: November 14, 2003

Laura A. Coruzzi (Reg. No. 30,742)
PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, N.Y. 10036-2711
(212) 790-9090

Enclosures

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Soff et al.

Confirmation No.: 2549

Serial No.: 09/500,397

Group Art Unit: 1642

Filed: February 8, 2000

Examiner: Minh-Tam B. Davis

For: METHODS AND COMPOSITIONS FOR GENERATING ANGIOSTATIN

Attorney Docket No.: 10561-005-999

REQUEST FOR CONTINUED EXAMINATION UNDER 37 C.F.R. 1.114

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Advisory Action mailed August 18, 2003 and in accordance with 37 C.F.R. § 1.114(d), please consider the remarks below. Applicants submit herewith: (1) a Request For Continued Examination Transmittal; and (2) a Petition for Extension of Time (in duplicate), accompanied by the appropriate provision authorizing payment of the required fee.

It is estimated that no other fee is required for filing this Reply. However, should the United States Patent and Trademark Office determine otherwise, please charge any additional fee to Pennie & Edmonds LLP Deposit Account No. 16-1150.